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(54) Apparatus for diagnosing cerebral infarction.

(57) A novel apparatus for diagnosing cerebral infarction uses a neural network, wherein plural sets of data previously obtained from healthy and sick person, each including an age, measured values of coagulo-fibrinolytic molecular markers (e.g. D-dimer, TAT and PAP), an index indicative of the state of cerebral infarction (e.g. 0 for healthy persons and 1 for sick persons) are repeatedly input into a neural network to let is learn the correlation to these characteristics and, thereafter, a set of data of a person to be diagnosed, including his age, measured values of the coagulo-fibrinolytic molecular markers and the like, are input into the neural network to obtain an index indicative of his state of cerebral infarction as a degree of dangerousness of cerebral infarction. This apparatus carries out a method which is significantly higher in accuracy as compared with the prior art methods using the same data.

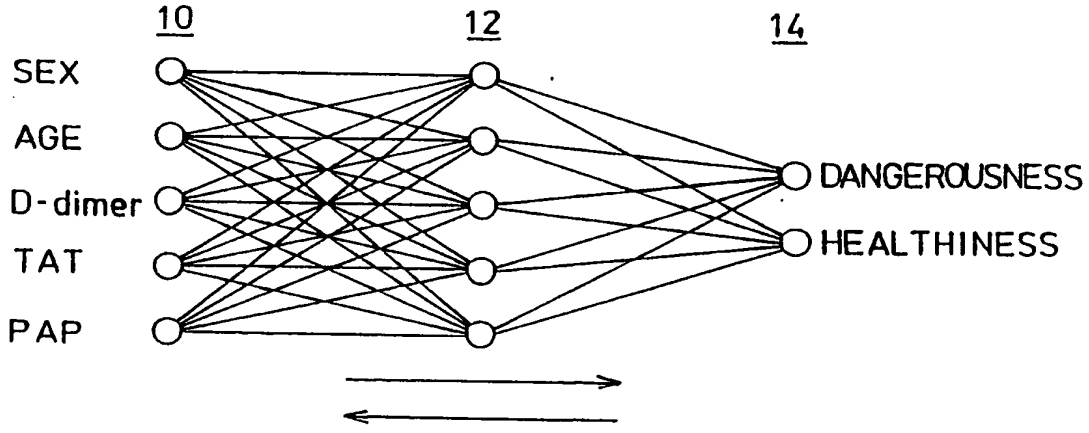

FIG. 1

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This invention relates to apparatus for carrying out a method of diagnosing cerebral infarction and, especially, to a novel and improved method of determining a degree of dangerousness of cerebral infarction using a neural network.

Cerebral infarction is referred to as a state such that a cerebral artery clogs for some reason and blood is reduced or even inhibited in the downstream tissue. About 20% of the cause of death of mankind is cerebrovascular disease and about 50% thereof is as a result of cerebral infarction. Cerebral infarction is classified into cerebral embolism and cerebral thrombosis. Cerebral embolism has no direct cause in the cerebral artery and becomes onset with coagulation of blood, albumin, fat or the like formed in the heart by heart disease such as atrial fibrillation or cardiomyopathy and flows into the cerebral artery to clog the same. In contrast, cerebral thrombosis is cause by a vascular endothelium incrassated by arteriosclerosis of the cerebral artery. The frequency of onset is higher in cerebral thrombosis than in cerebral embolism.

Current methods of diagnosing arteriosclerosis which may be a cause of cerebral embolism include indirect methods such as funduscopy, X-ray computed tomography, magnetic resonance imaging, pulse wave method or ultrasonic blood-flow measurement and direct methods such as angiography, angio-endoscopy or angio-echo, though neither method is satisfactory.

Recently, it has become possible to specifically measure values of coagulo-fibrinolytic molecular markers such as D-dimer or the like and, moreover, it has been found that these coagulo-fibrinolytic molecular markers have some relation to arteriosclerosis of the circulating system. For example, in the article of Suehiro et al. entitled "Clinical Usefulness of the Measurement of Plasma D-dimer Levels", the Japanese Journal of Clinical Pathology Society of Clinical Pathology, it is reported that the value of D-dimer which is a coagulo-fibrinolytic molecular marker is high in patients of cerebral infarction and it has a positive correlation with the age thereof and, moreover, that not only the D-dimer value but also the values of thrombin-antithrombin III complex (hereinunder referred to as TAT) and plasmin α_2 antiplasmin complex (hereinunder referred to as PAP) behave similarly.

Although this report suggests utility of the above-mentioned coagulo-fibrinolytic molecular marker values as an index of the state of cerebral infarction, it does not show any method of using the same to judge the state of cerebral infarction. It has been a general practice to use discriminant analysis or multiple regression analysis for calculating the degree of significance of linear relationship of such variations shown uncertain correlation or, in this case, the probability of ischemic stroke (hereinunder referred to as "dangerousness of cerebral infarction"). However, there is an unavoidable limit of accuracy in such basically linear method of discrimination.

Accordingly, an object of this invention is to provide a novel and improved apparatus for diagnosing cerebral infarction which can effect highly sensitive and accurate discrimination using the above-mentioned well-known variables.

Summary of invention

The present invention provides apparatus for carrying out a method which comprises the steps of repeatedly inputting plural sets of data to be learnt into a neural network to let the neural network learn the same, each set including an age, coagulo-fibrinolytic molecular marker measurements and an index indicative of cerebral infarction obtained from each of healthy persons and patients of cerebral infarction, and putting a set of data to be tested in the neural network to obtain the dangerousness of cerebral infarction of a person to be tested, the set of data including an age and coagulo-fibrinolytic molecular marker measurements obtained from the person to be tested.

The usable coagulo-fibrinolytic molecular markers are at least one of D-dimer, TAT and PAP and the set of data to be learnt and tested may include a value of sex distinction.

Now, the features and operational effects of this invention will be described in more detail below in connection with preferred embodiments with reference to the accompanying drawings.

Brief description of drawings

In the drawings:

Fig. 1 is a schematic view showing a neural network used in the embodiments of the invention for diagnosing cerebral infarction;

Fig. 2 is a flow chart showing a program for executing the method of the embodiment;

Fig. 3 is a histogram showing the result of diagnosis of cerebral infarction according to the embodiment;

Figs. 4 and 5 are histograms showing the results of diagnosis of cerebral infarction according to discriminant analysis and multiple regression analysis, respectively, for comparing with the result of Fig. 3; and

Fig. 6 is a diagram for explaining the histograms of Figs. 3 to 5.

Description of preferred embodiments

Referring to Fig. 1, the neural network is one using error back-propagation algorithm and has a three-layer structure consisting of an input layer 10, an intermediate or hidden layer 12 and an output layer 14. The input layer 10 has five neurons corresponding to five input data respectively consisting of the values indicative of sex distinction and age and the measurements of three coagulo-fibrinolytic molecular markers and the three coagulo-fibrinolytic molecular markers are D-dimer, TAT and PAP as described above. The three coagulo-fibrinolytic molecular marker measurements can be obtained by well-known methods and the values indicative of sex distinction and age are obtained as described below.

The output layers 14 has two neurons respectively corresponding to the values indicative of the degrees of healthiness and dangerousness regarding cerebral infarction (hereinunder referred to simply as "healthiness" and "dangerousness"). While the hidden layer 12 generally has three to ten neurons, this number is determined as five in the embodiments for the reason as described below. Therefore, the neural network has twelve neurons in total in the following embodiments.

The five neurons in the input layer 10 have synaptic junctions with the five neurons in the hidden layer 12 and the five neurons in the hidden layer 12 have synaptic junctions with the two neurons in the output layer 14. Therefore, the total number of the synaptic junctions is thirty-five (35=5x5+5x2). Each synaptic junction has a weight with respect to its input signal and the weight is previously established in an initializing step.

In the initialized neural network, a learning step S1 is executed first as shown in FIG. 2. In the learning step S1, the five kinds of input data are supplied to the input layer 10 as a set of learning inputs as described above, and the corresponding data of dangerousness and/or healthiness are supplied to the output layer 14 as teacher inputs. Then, the neural network calculates learning outputs of the dangerousness and/or healthiness from the learning inputs through the respective cynaptic junctions and compares them with the corresponding teacher inputs in the output layer 14. Next, the neural network turns back from the output layer 14 and calculates the internal states of the neurons of the respective layers toward the input layer 10 to correct the weights of the respective synaptic junctions so as to minimize the mean square errors between the learning inputs and the teacher inputs. This step is repeated for all sets of input data to finally determine the weights of the synaptic junctions. Thereafter, a testing step S2 is executed. In the testing step S2, data of the same items as the learning inputs obtained from a person to be tested are supplied to the input layer 10 to obtain the data of dangerousness and/or healthiness from the output layer 14.

The values of the input data to the neural network are not raw measured values of the respective characteristics but values from zero to one which are normalized in accordance with predetermined rules. In this embodiment, normalization was effected in accordance with the following rules.

(1) Sex distinction: Male = 0 and Female = 1.

(2) Age: Normalized age = Age(years)/100, where any age exceeding 100 years is assumed as 100 years.

(3) D-dimer: Normalized D-dimer value = D-dimer measurement(ng/ml)/500.0, where any measurement exceeding 500.0ng/ml is assumed as 500.0ng/ml.

(4) TAT: Normalized TAT value = TAT measurement (ng/ml)/16.0, where any measurement exceeding 16.0ng/ml is assumed as 16.0ng/ml.

(5) PAP: Normalized PAP value = PAP measurement (ng/ml)/1.5, where any measurement exceeding 1.6ng/ml is assumed as 1.5ng/ml.

(6) Dangerousness and healthiness: Maximun = 1 and minimum = 0.

The data for the learning inputs were obtained from 100 persons of cerebral infarction and 140 persons of non-cerebral infarction and the upper limits of D-dimer, TAT and PAP were determined with reference to their mean values plus twice their standard deviations.

Before commencing the learning step, it is necessary to determine the number of neurons in the hidden layer 12. If the number of neurons in the hidden layer 12 is small, no complexity of combination of the input data is transferred to the output layer 14. If it is too large on the contrary, the number of synaptic junctions increases to result in such disadvantages in that an excess time is needed for obtaining the output from the output layer 14 and the output value does not converge to its minimum value. The inventor used the above-mentioned learning input data to execute the learning step and evaluated the optimum number of neurons in the hidden layer 12 based upon the mean square error between the resultant output values of the respective neurons in the output layer 14 and the corresponding teacher input values, thereby obtaining five to seven. Thus, the number of neurons in the hidden layer 12 was determined as five in this embodiment.

The distribution of dangerousness obtained from the data of the above-mentioned 240 persons to be tested is expressed as a histogram as shown in FIG. 3. FIGS. 4 and 5 show histograms of dangerousness distributions

obtained from the same data by the above-mentioned discriminant analysis and multiple regression analysis, respectively. In the drawings, the abscissa shows the dangerousness of cerebral infarction and the ordinate shows the frequency (percent number) of persons of non-cerebral infarction (healthy-persons) upwards and the frequency of persons of cerebral infarction (patients) downwards.

FIG. 6 shows a partition diagram used for diagnosing cerebral infarction of each tested person based upon these histograms. The diagram includes a rectangle having the abscissa and ordinate of the histograms as both sides and being divided into four sections by the abscissa and a split line 16. The upper left section A1 shows a true negative region for healthy persons, the upper right section A2 shows a false positive region for healthy persons, the lower left section B1 shows a false negative region for sick persons and the lower right section B2 shows a true positive region for sick persons. The accuracy of diagnosis varies with the horizontal position of the split line 16.

Next, sensitivity, specificity, false positive rate and false negative rate in diagnosis of cerebral infarction were sought using the histograms of FIGS. 3, 4 and 5 and the diagram of FIG. 6, where sensitivity meant percent chance of diagnosing patients of cerebral infarction as positive and specificity meant percent chance of diagnosing healthy persons as negative. The results obtained with the split line 16 drafted at 0.4, 0.5 and 0.6 of dangerousness are shown in Tables 1, 2 and 3, respectively.

TABLE 1 (Spit line: 0.4)

FIG.	Sensitivity	Specificity	False positive rate	False negative rate
1	85.39%	91.39%	8.61%	14.61%
2	84.27%	86.09%	13.91%	15.73%
3	83.15%	86.09%	13.91%	16.85%

TABLE 2 (Split line: 0.5)

FIG.	Sensitivity	Specificity	False positive rate	False negative rate
1	83.15%	94.04%	5.96%	16.85%
2	83.15%	90.73%	9.27%	16.85%
3	69.66%	95.36%	4.64%	30.34%

TABLE 3 (Split line: 0.6)

FIG.	Sensitivity	Specificity	False positive rate	False negative rate
1	78.65%	94.70%	5.30%	21.35%
2	75.28%	94.70%	5.30%	24.72%
3	53.93%	96.69%	3.31%	46.07%

The followings can be said from the tables. (1) The inventive method and discriminant analysis have substantially same power when the split line is drafted at 0.5 of dangerousness. (2) In multiple regression analysis, its sensitivity drops extremely when the split line is drafted above 0.5 of dangerousness. (3) Sensitivity and specificity of the inventive method are high when the split line is drafted at 0.4 or 0.6 of dangerousness. Thus, it is found that there is less chance of presentation of medium degree of dangerousness in the inventive method and, therefore, it can result in sharp discrimination.

As a result of search for the false negative patients in the inventive method and discriminant analysis, it has been found that all of them are identical patients and the most of them are patients in acute period. Therefore, this false negativity might be caused by the difference of sick state between acute and chronic periods. Similarly, the false positive patients are other than those of disease of circulating system and some patients of hypertension are included therein. Since high blood pressure is a dangerous factor of arteriosclerosis, there would be no help for such diagnosis.

The above embodiment is presented only for the purpose of illustration and does not mean any limitation

of the invention. It is a matter of course that various modifications and changes can be added thereto within the scope of the invention as defined in the apended claims. For example, the values of age and respective coagulo-fibrinolytic molecular markers were used as mutally independent input data in the above embodiment. In practice, however, it has been known that the values of coagulo-fibrinolytic molecular markers increase with age, or there is some relation between the coagulo-fibrinolytic molecular markers and age. However, it is desirable that the respective input data are independent of each other. Therefore, it is also possible to make the coagulo-fibrinolytic molecular markers independent of the age by previously seeking a standard value of each coagulo-fibrinolytic molecular marker of a healthy person at each age and supplying the standard value subtracted from each coagulo-fibrinolytic molecular marker measurement into the input layer 10 as the value of said coagulo-fibrinolytic molecular marker and it is expected that learning effciency and diagnosing accuracy are thereby improved. While, in the above embodiment, sex distinction and three kinds of coagulo-fibrinolytic molecular markers, namely, D-dimer, TAT and PAP were used as the input data, it is enough to use at least one of the coagulo-fibrinolytic molecular markers together with the age. Moreover, a plurality of hidden layers may be used if necessary, through the hidden layer 12 was a single layer in the above embodiment.

Claims

1. Apparatus for diagnosing cerebral infarction comprising a neural network,

   means for supplying plural sets of learning data obtained from healthy persons and patients of cerebral infarction to the neural network to cause said neural network to learn the same, each said set including an age, a coagulo-fibrinolytic molecular marker measurement and an index indicative of cerebral infarction, and

   means for supplying a set of testing data obtained from a person to be tested to said neural network, the neural network being arranged to obtain an index indicative of cerebral infarction of said person to be tested as the output of said neural network, the neural network being arranged to obtain an index indicative of cerebral infarction of said person to be tested as the output of said neural network, said set of testing data including an age and a measurement of said coagulo-fibrinolytic molecular marker.

2. Apparatus as set forth in claim 1, characterized in that said coagulo-fibrinolytic molecular marker is D-dimer.

3. Apparatus as set forth in claim 1, characterized in that said coagulo-fibrinolytic molecular maker is thrombin-antithrombin III complex.

4. Apparatus as set forth in claim 1, characterized in that said coagulo-fibrinolytic molecular marker is plasmin-α_2-antiplasmin complex.

5. Apparatus as set forth in claim 1, characterized in that said learning data and said testing data further include an index indicative of sex distinction, respectively.

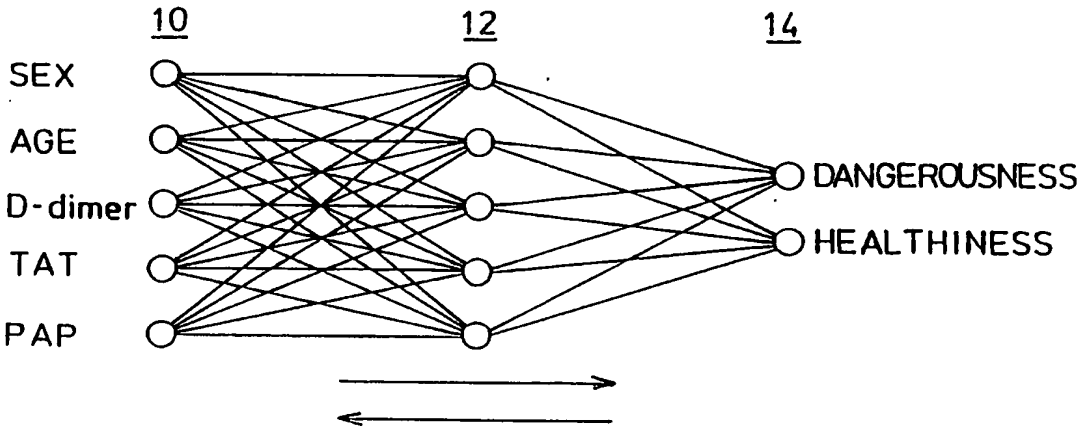
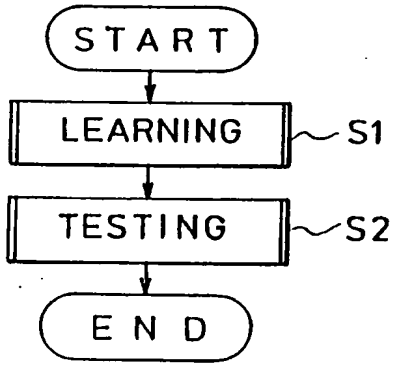


FIG. 1

FIG. 2



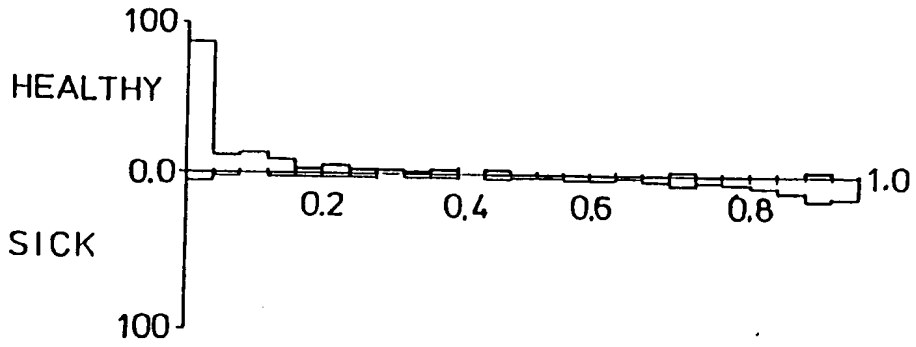


FIG. 3

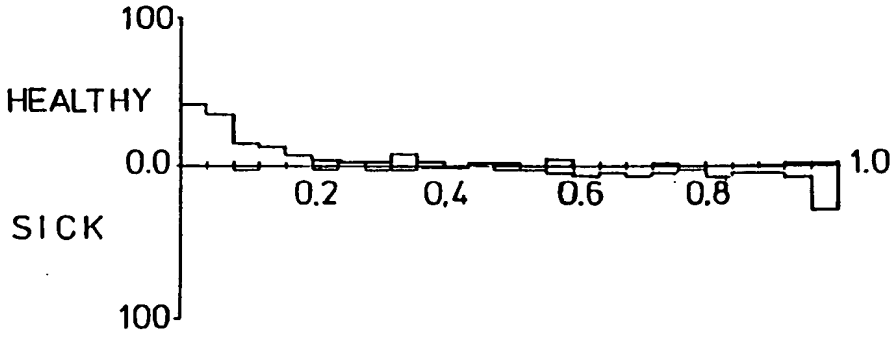


FIG. 4

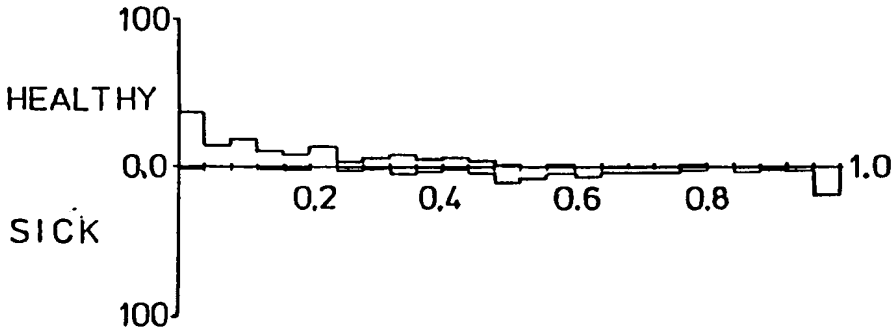


FIG. 5

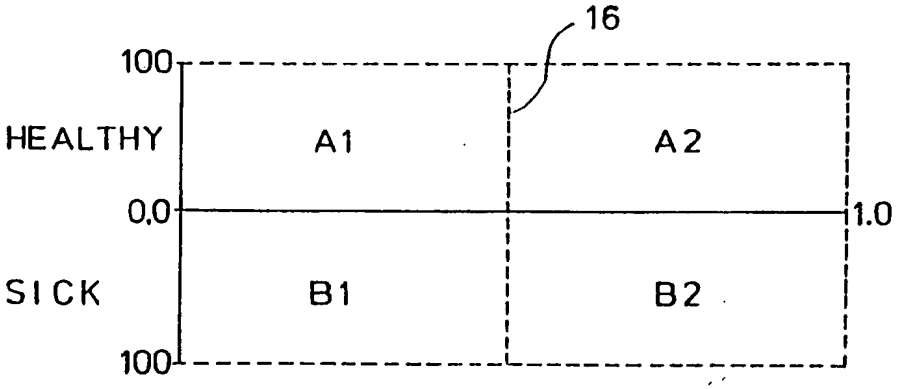


FIG. 6

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 92 31 1620

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 389 992 (TOSHIBA) * page 2, line 51 - page 6, line 36; figures 1,2 *	1	G06F15/20 G06F15/06
A	INTERNATIONAL JOINT CONFERENCE ON NEURAL NETWORKS vol. II, 8 July 1991, SEATTLE, US, pages 461 - 465 ICHIRO ENBUTSU ET AL 'Fuzzy Rule Extraction from a Multilayered Neural Network' * whole document *	1	
A	MEDICAL PROGRESS THROUGH TECHNOLOGY, vol. 13, no. 4, 1988, DORDRECHT, NL, pages 171 - 178 C.A.HOLZMANN ET AL 'A fuzzy model for medical diagnosis' * whole document *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5) G06F H03K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	05 MARCH 1993	WEIHS J.

CATEGORY OF CITED DOCUMENTS

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